SPECIFICATION AMENDMENTS

Please replace the bridging paragraph on page 6, line 26 to page 7, line 11, with the following rewritten paragraph:

With respect to the portion of the compound between the atom of Ar bound to L^2 and ring α, L^1 and L^2 are linkers which space the substituent Ar from ring α at a distance of 4.5-24Å, preferably 6-20Å, more preferably 7.5-10Å. The distance is measured from the center of the α ring to the atom of Ar to which the linker L^2 is attached. Typical, but nonlimiting, embodiments of L^1 and L^2 are CO and isosteres thereof, or optionally substituted isosteres, or longer chain forms. L^2, in particular, may be alkylene or alkenylene optionally substituted with noninterfering substituents or L^1 or L^2 may be or may include a heteroatom such as N, S or O. Such substituents include, but are not limited to, a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

Please replace the bridging paragraph on page 7, line 22 to page 8, line 5, with the following rewritten paragraph:

Each substituent on Ar is independently a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N, or is an inorganic residue. Preferred substituents include those selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~

alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members. More preferred substituents include halo, alkyl (1-4C) and more preferably, fluoro, chloro and methyl. These substituents may occupy all available positions of the aryl ring of Ar, preferably 1-2 positions, most preferably one position. These substituents may be optionally substituted with substituents similar to those listed. Of course some substituents, such as halo, are not further substituted, as known to one skilled in the art.

Please replace the bridging paragraph on page 8, line 18 to page 9, line 7, with the following rewritten paragraph:

R^4 represents a noninterfering substituent such as a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N. Preferably R^4 is alkyl, alkoxy, aryl, arylalkyl, aryloxy, heteroalkyl, heteroaryl, heteroarylalkyl, RCO, =O, acyl, halo, CN, OR, NRCOR, NR, wherein R is H, alkyl (preferably 1-4C), aryl, or hetero forms thereof. Each appropriate substituent is itself unsubstituted or substituted with 1-3 substituents. The substituents are preferably independently selected from a group that includes alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is =O or an oxime, oximeether, oximeester or ketal thereof. R^4 may occur m times on the ring; m is an integer of 0-4. Preferred embodiments of R^4 comprise alkyl (1-4C) especially two alkyl substituents and carbonyl. Most preferably R^4 comprises two methyl groups at positions 2 and 5 or 3 and 6 of a piperidinyl or piperazinyl ring or =O preferably at the 5-position of the ring. The substituted forms may be chiral and an isolated enantiomer may be preferred.

Please replace the paragraph on page 10, lines 1-14, with the following rewritten paragraph:

Preferably, the mandatory substituent CA or CR^8A is in the 3- position; regardless of which position this substituent occupies, the other position is CR^1, CR^1_2, NR^6 or N. CR^1 is preferred. Preferred embodiments of R^1 include hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^1 can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members. Most preferably, R^1 is H, alkyl, such as methyl, most preferably, the ring labeled α contains a double bond and CR^1 is CH or C-alkyl. Other preferable forms of R^1 include H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, ~~alkyl-OOR~~ alkyl-OOCR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

INDOLE-TYPE DERIVATIVES AS INHIBITORS OF p38 KINASE

This application claims priority under 35 U.S.C. § 119(e) to U.S. Serial No. (Attorney Docket No. 21900-30290.20) filed 9 May 2000 and to U.S. Serial No. 60/154,594 filed 17 September 1999. Priority is claimed under 35 U.S.C. § 120 with respect to U.S. Serial No. 09/316,761 filed 21 May 1999. The contents of these applications are incorporated herein by reference in their entirety.

Field of the Invention

The invention relates to treating various disorders associated with enhanced activity of kinase p38-α. More specifically, it concerns compounds that are related to indole-type derivatives coupled to piperazine- or piperidine-type moieties as useful in these methods.

Background Art

A large number of chronic and acute conditions have been recognized to be associated with perturbation of the inflammatory response. A large number of cytokines participate in this response, including IL-1, IL-6, IL-8 and TNF. It appears that the activity of these cytokines in the regulation of inflammation rely at least in part on the activation of an enzyme on the cell signaling pathway, a member of the MAP kinase family generally known as p38 and alternatively known as CSBP and RK. This kinase is activated by dual phosphorylation after stimulation by physiochemical stress, treatment with lipopolysaccharides or with proinflammatory cytokines such as IL-1 and TNF. Therefore, inhibitors of the kinase activity of p38 are useful anti-inflammatory agents.

Eye diseases associated with a fibroproliferative condition include retinal reattachment surgery accompanying proliferative vitreoretinopathy, cataract extraction with intraocular lens implantation, and post glaucoma drainage surgery.

PCT applications WO98/06715, WO98/07425, and WO 96/40143, all of which are incorporated herein by reference, describe the relationship of p38 kinase inhibitors with various disease states. As mentioned in these applications, inhibitors of p38 kinase are useful in treating a variety of diseases associated with chronic inflammation. These

applications list rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injuries such as neural trauma and ischemia, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases such as osteoporosis, graft-versus-host reaction, Crohn's Disease, ulcerative colitis including inflammatory bowel disease (IBD) and pyresis.

The above-referenced PCT applications disclose compounds which are p38 kinase inhibitors said to be useful in treating these disease states. These compounds are either imidazoles or are indoles substituted at the 3- or 4-position with a piperazine ring linked through a carboxamide linkage. Additional compounds which are conjugates of piperazines with indoles are described as insecticides in WO97/26252, also incorporated herein by reference.

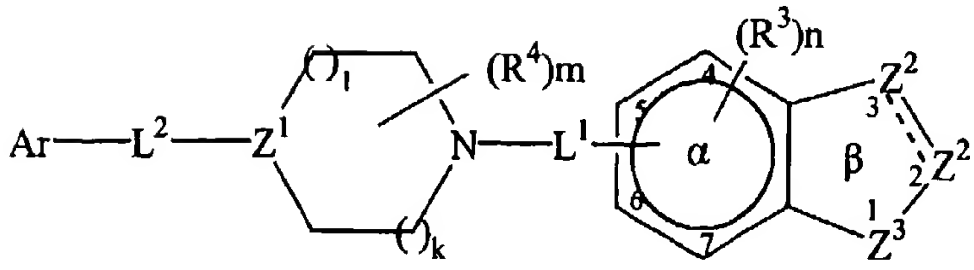
Certain aroyl/phenyl-substituted piperazines and piperidines which inhibit p38-α kinase are described in PCT publication WO00/12074 published 9 March 2000. In addition, indolyl substituted piperidines and piperazines which inhibit this enzyme are described in PCT publication No. WO99/61426 published 2 December 1999. Carbolene derivatives of piperidine and piperazine as p38-α inhibitors are described in PCT/US00/07934 filed 24 March 2000.

None of the foregoing patents describes the indole derivatives described herein which specifically inhibit p38-α.

Disclosure of the Invention

The invention is directed to methods and compounds useful in treating conditions that are characterized by enhanced p38-α activity. These conditions include inflammation, proliferative diseases, and certain cardiovascular disorders as well as Alzheimer's disease as further described below.

Compounds of the invention have been found to inhibit p38 kinase, the α-isoform in particular, and are thus useful in treating diseases mediated by these activities. The compounds of the invention are of the formula



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

 represents a single or double bond;

one Z^2 is CA or CR^8A and the other is CR^1, CR^1_2, NR^6 or N wherein each R^1, R^6 and R^8 is independently hydrogen or noninterfering substituent;

A is $-W_i-COX_jY$ wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a noninterfering substituent, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1;

Z^3 is NR^7 or O;

each R^3 is independently a noninterfering substituent;

n is 0-3;

each of L^1 and L^2 is a linker;

each R^4 is independently a noninterfering substituent;

m is 0-4;

Z^1 is CR^5 or N wherein R^5 is hydrogen or a noninterfering substituent;

each of l and k is an integer from 0-2 wherein the sum of l and k is 0-3;

Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring; and

the distance between the atom of Ar linked to L^2 and the center of the α ring is 4.5-24Å.

The invention is directed to methods of treating inflammation or proliferative conditions using these compounds. The invention is also directed to treating conditions associated with cardiac failure and Alzheimer's disease using the invention compounds.

Modes of Carrying Out the Invention

The compounds of formula (1) are useful in treating conditions which are characterized by overactivity of p38 kinase, in particular the α-isoform. Conditions "characterized by enhanced p38-α activity" include those where this enzyme is present in increased amount or wherein the enzyme has been modified to increase its inherent activity, or both. Thus, "enhanced activity" refers to any condition wherein the effectiveness of these proteins is undesirably high, regardless of the cause.

The compounds of the invention are useful in conditions where p38-α kinase shows enhanced activity. These conditions are those in which fibrosis and organ sclerosis are caused by, or accompanied by, inflammation, oxidation injury, hypoxia, altered temperature or extracellular osmolarity, conditions causing cellular stress, apoptosis or necrosis. These conditions include ischemia-reperfusion injury, congestive heart failure, progressive pulmonary and bronchial fibrosis, hepatitis, arthritis, inflammatory bowel disease, glomerular sclerosis, interstitial renal fibrosis, chronic scarring diseases of the eyes, bladder and reproductive tract, bone marrow dysplasia, chronic infectious or autoimmune states and traumatic or surgical wounds. These conditions, of course, would be benefited by compounds which inhibit p38-α. Methods of treatment with the compounds of the invention are further discussed below.

The Invention Compounds

The compounds useful in the invention are derivatives of indole-type compounds containing a mandatory substituent, A, at a position corresponding to the 2- or 3- position of indole. In general, an indole-type nucleus is preferred, although alternatives within the scope of the invention are also illustrated below.

In the description above, certain positions of the molecule are described as permitting "noninterfering substituents." This terminology is used because the substituents in these positions generally speaking are not relevant to the essential activity of the molecule taken as a whole. A wide variety of substituents can be employed in these positions, and it is well within ordinary skill to determine whether any particular arbitrary substituent is or is not "noninterfering."

As used herein, a "noninterfering substituent" is a substituent which leaves the ability of the compound of formula (1) to inhibit p38-α activity qualitatively intact. Thus, the substituent may alter the degree of inhibition of p38-α. However, as long as the compound of formula (1) retains the ability to inhibit p38-α activity, the substituent will be classified as "noninterfering." A number of assays for determining the ability of any compound to inhibit p38-α activity are available in the art. A whole blood assay for this evaluation is illustrated below: the gene for p38-α has been cloned and the protein can be prepared recombinantly and its activity assessed, including an assessment of the ability of an arbitrarily chosen compound to interfere with this activity. The essential features of the molecule are tightly defined. The positions which are occupied by "noninterfering substituents" can be substituted by conventional organic moieties as is understood in the art. It is irrelevant to the present invention to test the outer limits of such substitutions. The essential features of the compounds are those set forth with particularity herein.

In addition, L^1 and L^2 are described herein as linkers. The nature of such linkers is less important that the distance they impart between the portions of the molecule. Typical linkers include alkylene, *i.e.* $(CH_2)_n$-R; alkenylene - *i.e.*, an alkylene moiety which contains a double bond, including a double bond at one terminus. Other suitable linkers include, for example, substituted alkylenes or alkenylenes, carbonyl moieties, and the like.

As used herein, "hydrocarbyl residue" refers to a residue which contains only carbon and hydrogen. The residue may be aliphatic or aromatic, straight-chain, cyclic, branched, saturated or unsaturated. The hydrocarbyl residue, when so stated however, may contain heteroatoms over and above the carbon and hydrogen members of the substituent residue. Thus, when specifically noted as containing such heteroatoms, the hydrocarbyl residue may also contain carbonyl groups, amino groups, hydroxyl groups and the like, or contain heteroatoms within the "backbone" of the hydrocarbyl residue.

As used herein, "inorganic residue" refers to a residue that does not contain carbon. Examples include, but are not limited to, halo, hydroxy, NO_2 or NH_2.

As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight- and branched-chain and cyclic monovalent substituents. Examples include methyl, ethyl, isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butynyl, and the like. Typically,

the alkyl, alkenyl and alkynyl substituents contain 1-10C (alkyl) or 2-10C (alkenyl or alkynyl). Preferably they contain 1-6C (alkyl) or 2-6C (alkenyl or alkynyl). Heteroalkyl, heteroalkenyl and heteroalkynyl are similarly defined but may contain 1-2 O, S or N heteroatoms or combinations thereof within the backbone residue.

As used herein, "acyl" encompasses the definitions of alkyl, alkenyl, alkynyl and the related hetero-forms which are coupled to an additional residue through a carbonyl group.

"Aromatic" moiety refers to a monocyclic or fused bicyclic moiety such as phenyl or naphthyl; "heteroaromatic" also refers to monocyclic or fused bicyclic ring systems containing one or more heteroatoms selected from O, S and N. The inclusion of a heteroatom permits inclusion of 5-membered rings as well as 6-membered rings. Thus, typical aromatic systems include pyridyl, pyrimidyl, indolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl and the like. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system is included in this definition. Typically, the ring systems contain 5-12 ring member atoms.

Similarly, "arylalkyl" and "heteroalkyl" refer to aromatic and heteroaromatic systems which are coupled to another residue through a carbon chain, including substituted or unsubstituted, saturated or unsaturated, carbon chains, typically of 1-6C. These carbon chains may also include a carbonyl group, thus making them able to provide substituents as an acyl moiety.

When the compounds of Formula 1 contain one or more chiral centers, the invention includes optically pure forms as well as mixtures of stereoisomers or enantiomers

With respect to the portion of the compound between the atom of Ar bound to L^2 and ring α, L^1 and L^2 are linkers which space the substituent Ar from ring α at a distance of 4.5-24Å, preferably 6-20Å, more preferably 7.5-10Å. The distance is measured from the center of the α ring to the atom of Ar to which the linker L^2 is attached. Typical, but nonlimiting, embodiments of L^1 and L^2 are CO and isosteres thereof, or optionally substituted isosteres, or longer chain forms. L^2, in particular, may be alkylene or

alkenylene optionally substituted with noninterfering substituents or L^1 or L^2 may be or may include a heteroatom such as N, S or O. Such substituents include, but are limited to, a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

Isosteres of CO and CH_2, include SO, SO_2, or CHOH. CO and CH_2 are preferred.

Thus, L^2 is substituted with 0-2 substituents. Where appropriate, two optional substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated hydrocarbyl ring that includes 0-3 heteroatoms such as O, S and/or N and which contains 3 to 8 members. Two optional substituents on L^2 can be joined to form a carbonyl moiety which can be subsequently converted to an oxime, an oximeether, an oximeester, or a ketal.

Ar is aryl, heteroaryl, including 6-5 fused heteroaryl, cycloaliphatic or cycloheteroaliphatic that can be optionally substituted. Ar is preferably optionally substituted phenyl.

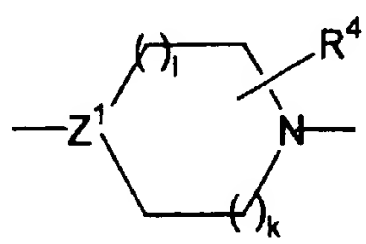
Each substituent on Ar is independently a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N, or is an inorganic residue. Preferred substituents include those selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members. More preferred substituents

Sub C2

include halo, alkyl (1-4C) and more preferably, fluoro, chloro and methyl. These substituents may occupy all available positions of the aryl ring of Ar, preferably 1-2 positions, most preferably one position. These substituents may be optionally substituted with substituents similar to those listed. Of course some substituents, such as halo, are not further substituted, as known to one skilled in the art.

Two substituents on Ar can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

Between L^1 and L^2 is a piperidine-type moiety of the following formula:



Z^1 is CR^5 or N wherein R^5 is H or a noninterfering substituent. Each of l and k is an integer from 0-2 wherein the sum of l and k is 0-3. The noninterfering substituents R^5 include, without limitation, halo, alkyl, alkoxy, aryl, arylalkyl, aryloxy, heteroaryl, acyl, carboxy, or hydroxy. Preferably, R^5 is H, alkyl, OR, NR_2, SR or halo, where R is H or alkyl. Additionally, R^5 can be joined with an R^4 substituent to form an optionally substituted non-aromatic saturated or unsaturated hydrocarbyl ring which contains 3-8 members and 0-3 heteroatoms such as O, N and/or S. Preferred embodiments include compounds wherein Z^1 is CH or N, and those wherein both l and k are 1.

R^4 represents a noninterfering substituent such as a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and N. Preferably R^4 is alkyl, alkoxy, aryl, arylalkyl, aryloxy, heteroalkyl, heteroaryl, heteroarylalkyl, RCO, =O, acyl, halo, CN, OR, NRCOR, NR, wherein R is H, alkyl (preferably 1-4C), aryl, or hetero forms thereof. Each appropriate substituent is itself unsubstituted or substituted with 1-3 substituents. The substituents are preferably independently selected from a group that includes alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can

be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is =O or an oxime, oximeether, oximeester or ketal thereof. R^4 may occur m times on the ring; m is an integer of 0-4. Preferred embodiments of R^4 comprise alkyl (1-4C) especially two alkyl substituents and carbonyl. Most preferably R^4 comprises two methyl groups at positions 2 and 5 or 3 and 6 of a piperidinyl or piperazinyl ring or =O preferably at the 5-position of the ring. The substituted forms may be chiral and an isolated enantiomer may be preferred.

R^3 also represents a noninterfering substituent. Such substituents include hydrocarbyl residues (1-6C) containing 0-2 heteroatoms selected from O, S and/or N and inorganic residues. n is an integer of 0-3, preferably 0 or 1. Preferably, the substituents represented by R^3 are independently halo, alkyl, heteroalkyl, OCOR, OR, NRCOR, SR, or NR_2, wherein R is H, alkyl, aryl, or heteroforms thereof.. More preferably R^3 substituents are selected from alkyl, alkoxy or halo, and most preferably methoxy, methyl, and chloro. Most preferably, n is 0 and the α ring is unsubstituted, except for L^1 or n is 1 and R^3 is halo or methoxy.

In the ring labeled β, Z^3 may be NR^7 or O - *i.e.*, the compounds may be related to indole or benzofuran. If C^3 is NR^7, preferred embodiments of R^7 include H or optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, NR_2, OR, alkyl-SR, alkyl-SOR, alkyl-SO_2R, alkyl-OCOR, alkyl-COOR, alkyl-CN, alkyl-$CONR_2$, or R_3Si, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof. More preferably, R^7 is hydrogen or is alkyl (1-4C), preferably methyl or is acyl (1-4C), or is COOR wherein R is H, alkyl, alkenyl of aryl or hetero forms thereof. R^7 is also preferably a substituted alkyl wherein the preferred substituents are form ether linkages or contain sulfinic or sulfonic acid moieties. Other preferred substituents include sulfhydryl substituted alkyl substituents. Still other preferred substituents include $CONR_2$ wherein R is defined as above.

It is preferred that the indicated dotted line represents a double bond; however, compounds which contain a saturated β ring are also included within the scope of the invention.

Preferably, the mandatory substituent CA or CR^8A is in the 3- position; regardless of which position this substituent occupies, the other position is CR^1, CR^1_2, NR^6 or N. CR^1 is preferred. Preferred embodiments of R^1 include hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^1 can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members. Most preferably, R^1 is H, alkyl, such as methyl, most preferably, the ring labeled α contains a double bond and CR^1 is CH or C-alkyl. Other preferable forms of R^1 include H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

While the position not occupied by CA is preferred to include CR^1, the position can also be N or NR^6. While NR^6 is less preferred (as in that case the ring labeled β would be saturated), if NR^6 is present, preferred embodiments of R^6 include H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

Preferably, CR^8A or CA occupy position 3- and preferably Z^2 in that position is CA. However, if the β ring is saturated and R^8 is present, preferred embodiments for R^8 include H, halo, alkyl, alkenyl and the like. Preferably R^8 is a relatively small substituent corresponding, for example, to H or lower alkyl 1-4C.

A is $-W_i-COX_jY$ wherein Y is COR^2 or an isostere thereof and R^2 is a noninterfering substituent. Each of W and X is a spacer and may be, for example, optionally substituted alkyl, alkenyl, or alkynyl, each of i and j is 0 or 1. Preferably, W and X are unsubstituted. Preferably, j is 0 so that the two carbonyl groups are adjacent to each other. Preferably, also, i is 0 so that the proximal CO is adjacent the ring. However, compounds wherein the proximal CO is spaced from the ring can readily be prepared by

Sub B Cont.

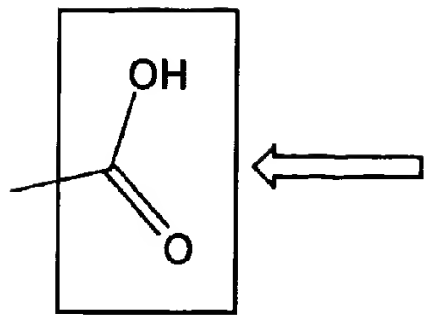
selective reduction of an initially glyoxal substituted β ring. In the most preferred embodiments of the invention, the α/β ring system is an indole containing CA in position 3- and wherein A is $COCR^2$.

The noninterfering substituent represented by R^2, when R^2 is other than H, is a hydrocarbyl residue (1-20C) containing 0-5 heteroatoms selected from O, S and/or N or is an inorganic residue. Preferred are embodiments wherein R^2 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or wherein R^2 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined.

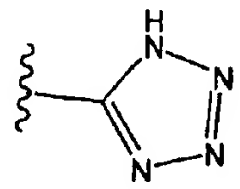
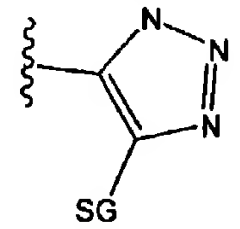
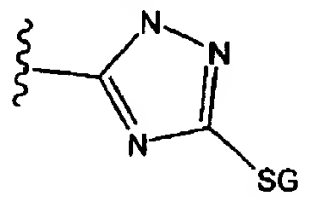
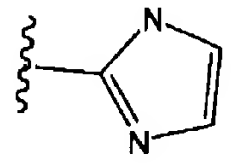
Other preferred embodiments of R^2 are H, heteroarylalkyl, $-NR_2$, heteroaryl, -COOR, $-NHRNR_2$, heteroaryl-COOR, heteroaryloxy, -OR, heteroaryl-NR_2, -NROR and alkyl. Most preferably R^2 is isopropyl piperazinyl, methyl piperazinyl, dimethylamine, piperazinyl, isobutyl carboxylate, oxycarbonylethyl, morpholinyl, aminoethyldimethylamine, isobutyl carboxylate piperazinyl, oxypiperazinyl, ethylcarboxylate piperazinyl, methoxy, ethoxy, hydroxy, methyl, amine, aminoethyl pyrrolidinyl, aminopropanediol, piperidinyl, pyrrolidinyl-piperidinyl, or methyl piperidinyl.

Isosteres of COR^2 as represented by Y are defined as follows.

The isosteres have varying lipophilicity and may contribute to enhanced metabolic stability. Thus, Y, as shown, may be replaced by the isosteres in Table 1.



R plac d by Acid Isost r s

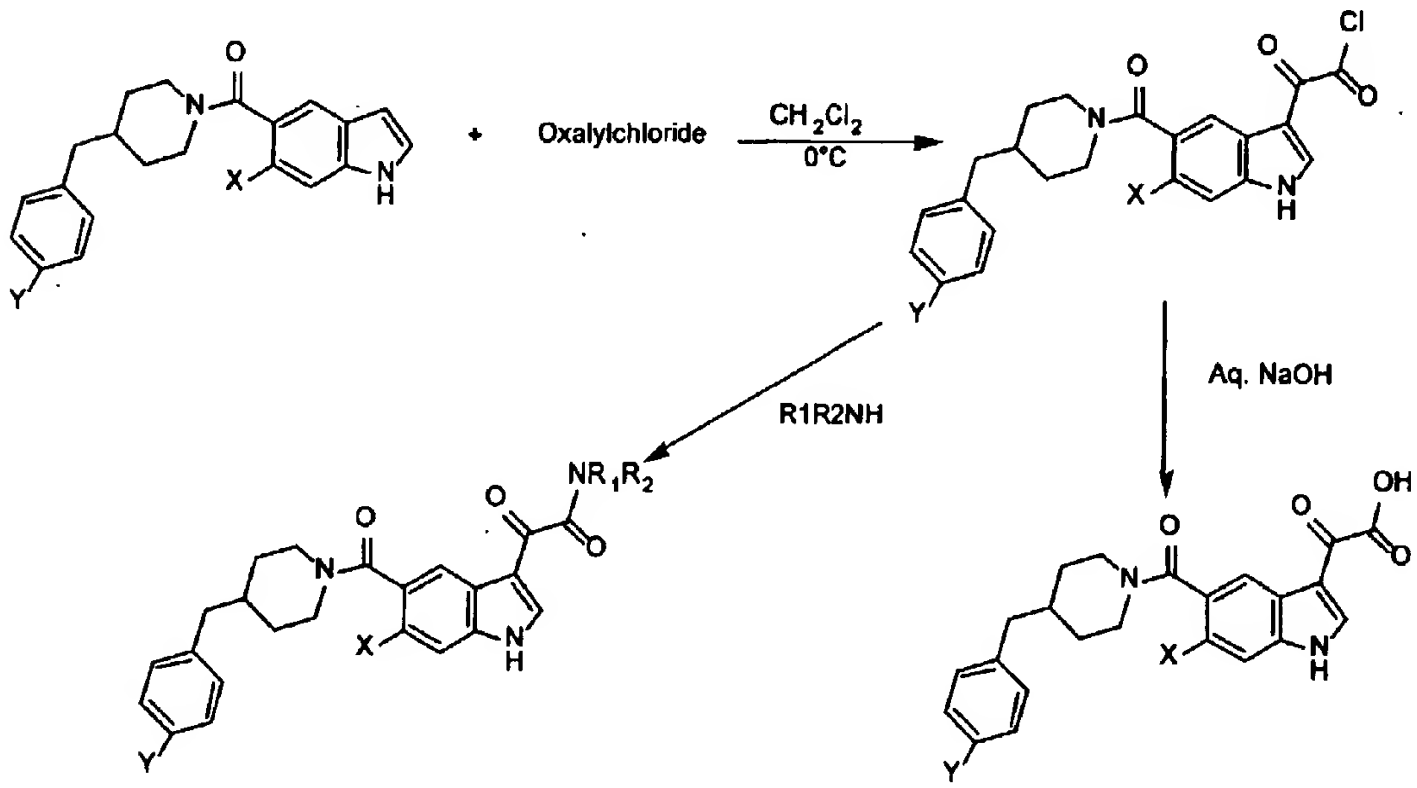
Table 1 - Acid Isosteres		
Names of Groups	**Chemical Structures**	**Substitution Groups (SG)**
tetrazole		n/a
1,2,3-triazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2; CF_3; CN; COOMe
1,2,4-triazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2
imidazole		H; SCH_3; $COCH_3$; Br; $SOCH_3$; SO_2CH_3; NO_2

Thus, isosteres include tetrazole, 1,2,3-triazole, 1,2,4-triazole and imidazole.

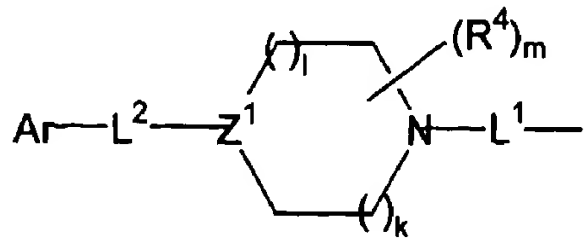
The compounds of formula (1) may be supplied in the form of their pharmaceutically acceptable acid-addition salts including salts of inorganic acids such as hydrochloric, sulfuric, hydrobromic, or phosphoric acid or salts of organic acids such as acetic, tartaric, succinic, benzoic, salicylic, and the like. If a carboxyl moiety is present on the compound of formula (1), the compound may also be supplied as a salt with a pharmaceutically acceptable cation.

Synthesis of the Invention Compounds

The following Reaction Scheme is illustrative of the conversion of a 4-benzyl piperidinyl-indole-5-carboxamide to the glyoxalic acid compounds of the invention and derivatives thereof.

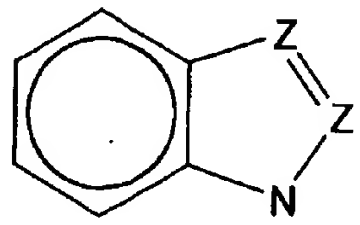


Of course, the 4-benzyl piperidinyl carbonyl of the illustration at position 5 may be generalized as



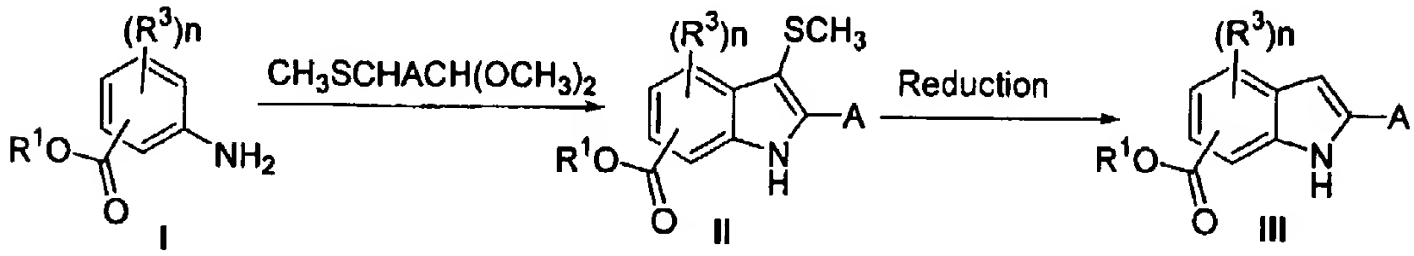
and the glyoxal type substituent at position 3 can be generalized to W_iCOXjY.

Similarly, embodiments wherein the indole-type moiety is



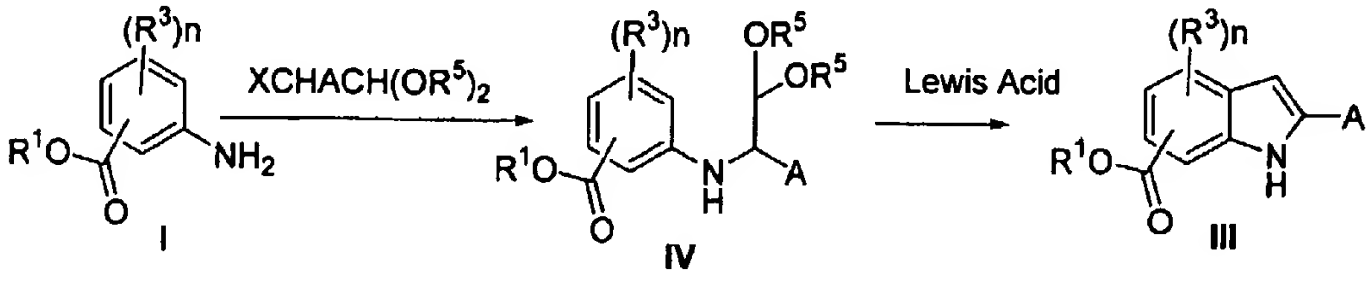
can be used in these schemes. Methods to synthesize the compounds of the invention are, in general, known in the art.

The following general schemes illustrate such methods.



Scheme 1

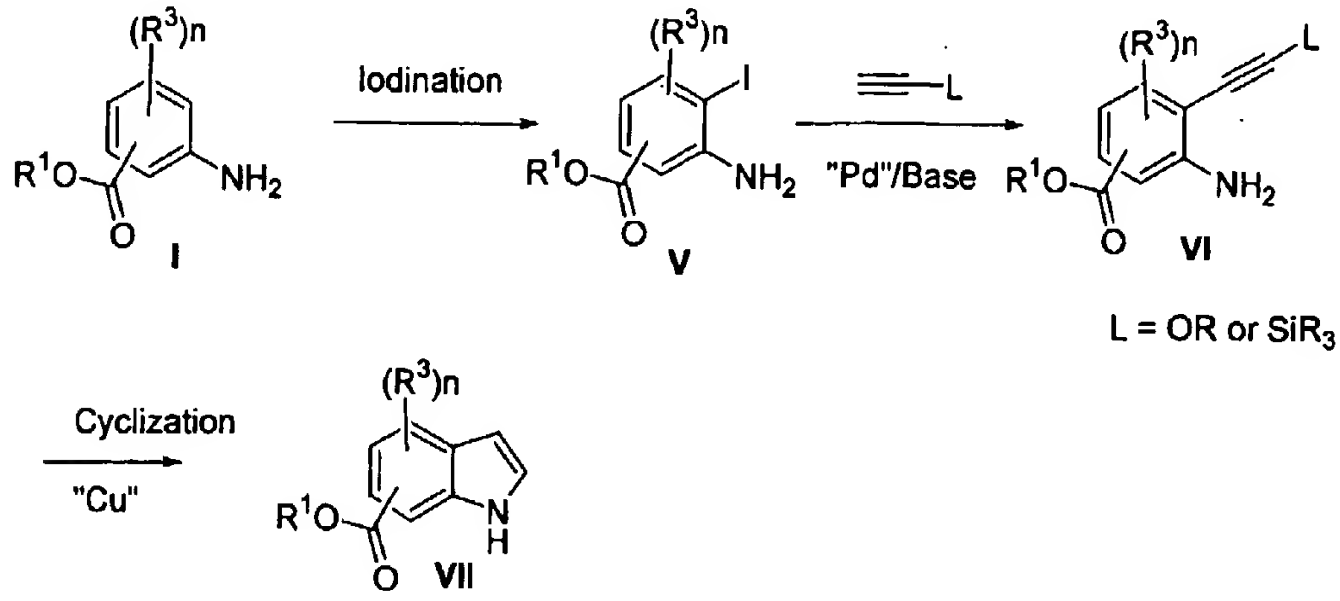
Substituted amino benzoic acid esters such as **I** can be treated with reagents such as thiomethylacetaldehyde dimethyl acetal and N-chlorosuccinamide in methylene chloride at low temperature followed by the treatment with a base such as triethylamine at reflux in methylene chloride, dichloroethane or chloroform to give indoles **II**, Scheme 1. Treatment with reagents such as Raney-Nickel in an appropriate solvent such as ethanol, methanol or isopropanol will yield the corresponding indole carboxylic acid ester which when hydrolyzed under base conditions will give the desired substituted indole carboxylic acid.



Scheme 2

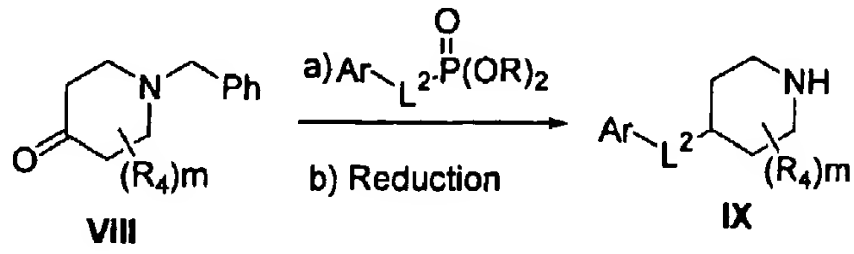
Alternatively, substituted amino benzoic acid esters **I** can be converted to the ketals **IV**, Scheme 2, with an appropriate aldehyde under conditions of reductive alkylation with reagents such as sodium triacetoxyborohydride in acetic acid in the presence of sodium sulfate. The amines can then be treated with lewis acids such as

aluminum chloride, titanium chloride, BF_3-etherate in dichloromethane or dichloroethane, under reflux to give the corresponding substituted indole methyl esters, with appropriate substitutions.



Scheme 3

Another method could involve the treatment of the substituted amino benzoic acid esters **I** with iodine and sodium periodate in an appropriate solvent such as dimethyformamide, to give the corresponding iodo aniline **V**, Scheme 3. This can be coupled with an acetylene such as trimethyl silyl acetylene or ethylethynyl ether in the presence of an appropriate catalysts such as palladium and copper and a base such as triethylamine to give the silyl coupled product such as **VI**. Subsequent cyclization in a solvent such as dimethylformamide and in the presence of a catalyst such as copper iodide would give the appropriately substituted indoles **VII**.



Scheme 4

Synthesis of the required piperidines can be achieved by treating an appropriate piperidone such as **VIII**, Scheme 4, with substituted benzyl phosphonate esters in the presence of a base such as sodium hydride to give alkenes which can be reduced to the corresponding substituted 4-benzylpiperidine such as **IX**. The hydrogenations are